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## Executive Summary

| Basic questions which require data-driven answers | Project Salus provides answers to these questions |
| --- | --- |

Is vaccine effectiveness (VE) **waning** over time?

Is VE **reduced** for the **Delta variant**?

Does the need vary by **sub-population**?

- VE of both mRNA vaccines appears to wane over time in this large 5.6M US-based 65 & over vaccinated cohort

- Risk of breakthrough hospitalization increases with time elapsed since mRNA vaccination with odds ratio increasing to 2.5 at 6 months post vaccination

- VE against Delta breakthrough hospitalization (62%) exceeds VE against Delta infection (41%)

- Prior COVID-19 infection has a major protective effect against breakthrough hospitalization

- Older age groups (75-84 & 85 and older) experienced further reduction in vaccine protection against hospitalization

- Hospitalization rate (21% vs 32%) and death rate (2% vs 12%) of breakthrough infections lower than rates observed in Covid-19 cases in pre-vaccination pandemic phase in 2020
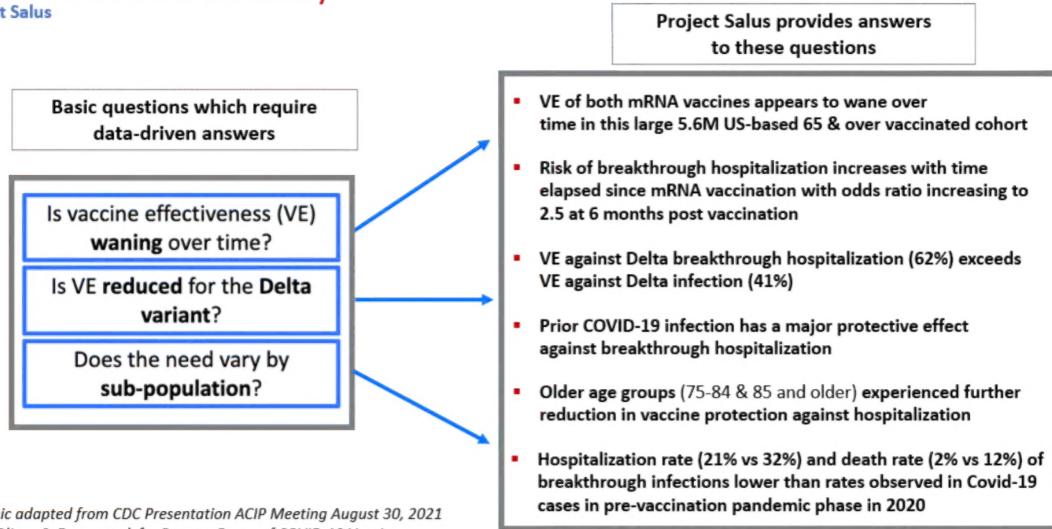
*Graphic adapted from CDC Presentation ACIP Meeting August 30, 2021*
*Oliver, S. Framework for Booster Doses of COVID-19 Vaccines*

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*JAIC is the US Department of Defense Joint Artificial Intelligence Center*

## Effectiveness of mRNA COVID-19 Vaccines Against the Delta Variant Among 5.6M Medicare Beneficiaries 65 Years and Older

### Weekly update of September 28, 2021

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Salus Platform for COVID-19 Analyses

VE Study Attributes

Other Platform Applications

**Cohort**

20M Medicare beneficiaries nationwide with 16M individuals 65 years and older

**Exposure**

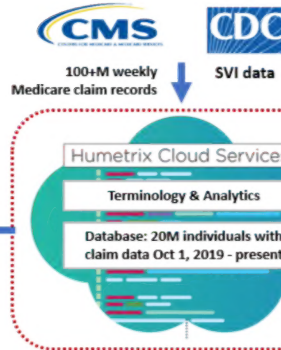5.6M fully vaccinated with 2.7M Pfizer and 2.9M Moderna

**Period of study**

January - August 21 2021

**Breakthrough Key Metrics**

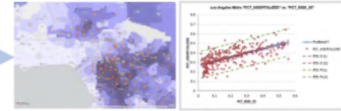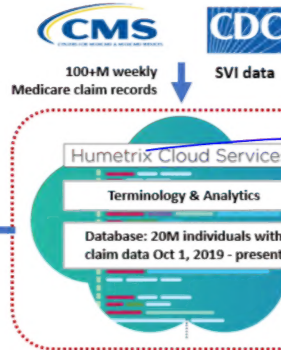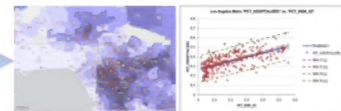161K Breakthrough cases

33K Breakthrough hospitalizations

10.4K requiring ICU admissions

CMS · CDC

100+M weekly Medicare claim records · SVI data

Humetrix Cloud Services

Terminology & Analytics

Database: 20M individuals with claim data Oct 1, 2019 - present

Nationwide Mapping of COVID-19 Outcomes Hospitalizations, ICU, Ventilator Rx, Deaths

Disease Risk Models with Population Risk Profiling: Severe COVID-19 risk with Validation with Hospitalization Rates

Vaccination Mapping overlaid on severe COVID-19 risk

* Medicare data and Humetrix software are hosted in a secure government enclave of the Department of Defense

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## Salus Breakthrough Analysis Methodology and Limitations

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- **Breakthrough case definition**: new COVID-19 diagnosis (by COVID-19 ICD-10 code) occurring no earlier than 2-weeks post the second vaccine dose (see appendix for more details on case definition)

- **Breakthrough analysis methodology**: to estimate weekly breakthrough cases and hospitalizations we multiplied our Medicare claim-based weekly breakthrough case counts and hospitalization counts by the corresponding weekly ratio of the claims-based vaccination rate to the CDC vaccination rate to compensate for missing COVID-19 vaccination data from Medicare claim data  (Medicare claims only provide ~45% of the published CDC vaccination rate in the 65 and over age group)

- **Breakthrough data limitations**:
  - Possible overestimation of breakthrough rates due to breakthroughs clinically defined with a COVID-19 diagnosis but not confirmed by PCR or antigen test (unavailable in claim data)
  - Possible overestimation of breakthrough rates due to assuming identical breakthrough rates between individuals with claim-based vaccination data and those lacking vaccination data in their claims
  - Overestimation of breakthrough rates would lead to underestimating vaccine VE against breakthrough infections and breakthrough hospitalizations

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## COVID-19 Case Definitions
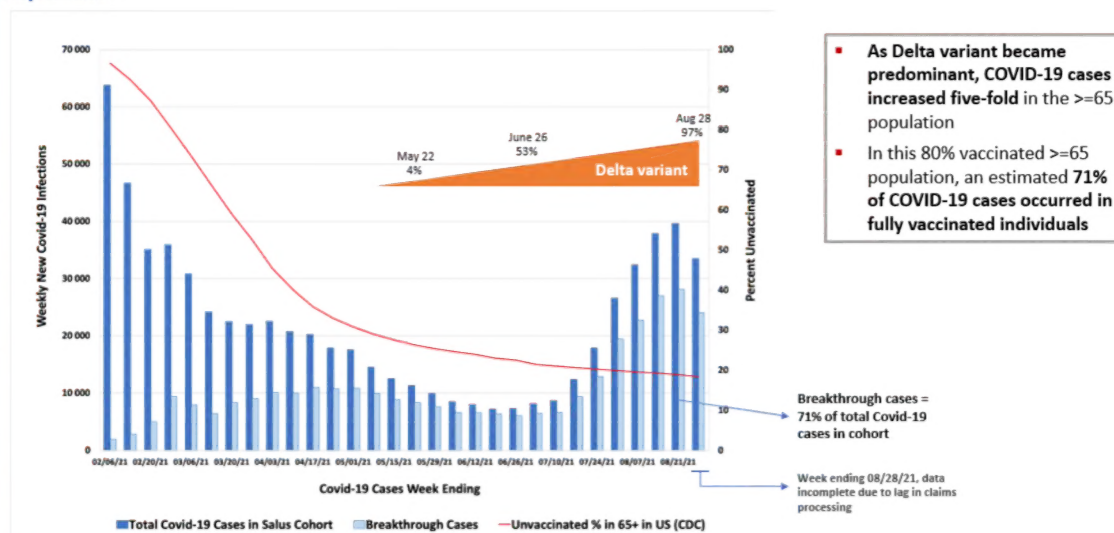
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- **COVID-19 case definition**: COVID-19 ICD-10-CM code U071 found in any claim type. Date of diagnosis based on first claim with U071. Note: 29% have either a COVID-19 PCR or antigen test in a claim.

- **COVID-19 breakthrough infection definition**: COVID-19 diagnosis more than 2 weeks after second dose of mRNA vaccine or single dose of J&J vaccine with no COVID-19 ICD-10 code U071 between first and second dose of mRNA vaccine. Note: 36% of  breakthrough cases have either a COVID-19 PCR or antigen test in a claim.

- **COVID-19 hospitalization definitions**: (1) Inpatient claim with primary admitting diagnosis ICD-10-C code U071 with data of admission within 14 days after COVID-19 diagnosis or date of discharge within 10 days of post hospitalization COVID-19 diagnosis OR (2) Carrier claim with ICD10 code U071 and place of service code = 21 and date of service either 14 days after COVID-19 diagnosis or 10 days before COVID-19 diagnosis.

- **COVID-19 associated death definitions**: (1) Inpatient claim patient discharge status code = 41 (expired in facility) OR (2) MBSF file Date of Death are within 60 days of COVID-19 diagnosis. 85% of COVID-19 deaths using this definition occurred within 30 days and 72% within 20 days of COVID-19 diagnosis

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# Key Breakthrough vs. Pre-Vaccination COVID-19 Metrics

**Among 5.6M fully vaccine immunized Salus cohort members aged 65 and older** (2.7M Pfizer and 2.9M Moderna), as of September 10, 2021:

- **2.9% cumulative breakthrough rate**

- **21% hospitalization rate** in breakthrough infections, <u>reduced by one third of 32% hospitalization rate</u> March – December 2020

- **31% breakthrough hospitalizations include ICU care,** equivalent to 32% ICU rate March – December 2020

- **2.1% death rate** in breakthrough infections, <u>reduced six-fold from 12% death rate</u> March – December 2020

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# Total & Breakthrough Cases in the 65 Years and Older Salus Cohort



- **As Delta variant became predominant, COVID-19 cases increased five-fold** in the >=65 population

- In this 80% vaccinated >=65 population, an estimated **71% of COVID-19 cases occurred in fully vaccinated individuals**

Breakthrough cases = 71% of total Covid-19 cases in cohort

Week ending 08/28/21, data incomplete due to lag in claims processing

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*CDC data: % of SARS-CoV-2 genomes sequenced*

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## Is mRNA Vaccine Effectiveness Against Delta Breakthrough Infection Waning Over Time in 65 Years and Older Salus Cohort?
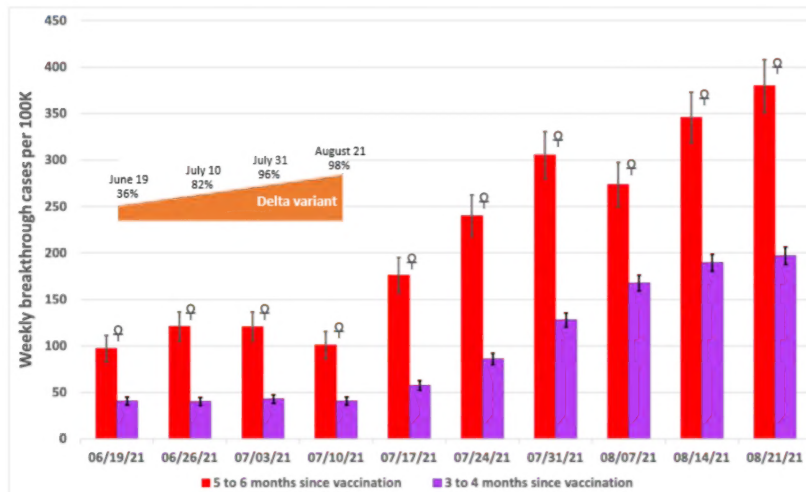


- Breakthrough infection rates 5-6 months post vaccination are twice as high as 3-4 months post vaccination

| 95% CI

⚥ Breakthrough infection rates 5-6 months since vaccination > 3-4 months since vaccination
P < 0.001

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## Age Distribution of Vaccinated Groups in the 65 Years and Older Cohort

| Vaccinee Group | | |
|---|---|---|
| **5-6 months post vaccination** | | |
| age groups | 65 to 74 | 24% |
| | 75 to 84 | 33% |
| | 85 & older | 43% |
| **3-4 months post vaccination** | | |
| age groups | 65 to 74 | 51% |
| | 75 to 84 | 35% |
| | 85 & older | 14% |

- Could higher proportion of 85 years and older members in first vaccinated group explain reduced VE?

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## Does Age Affect Vaccine Effectiveness Against Breakthrough Infections in the 65 Years and Older Cohort?
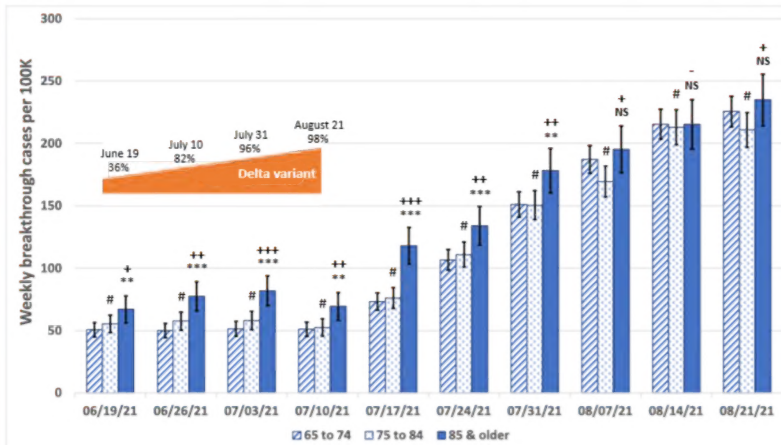


- **Age has a minor contribution to the reduced vaccine protection** seen in the group vaccinated 5-6 months ago

95% CI

| | Over 85 > 75 to 84 | Over 85 > 65 to 74 | 75 to 84 > 65 to 74 |
|---|---|---|---|
| P < 0.001 | +++ | *** | none |
| P < 0.01 | ++ | ** | none |
| P < 0.05 | + | none | none |
| P > 0.05 | - | NS | # |

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## Are There Differences in Waning Effectiveness Between Pfizer-BioNTech and Moderna Vaccines in the 65 Years and Older Cohort ?
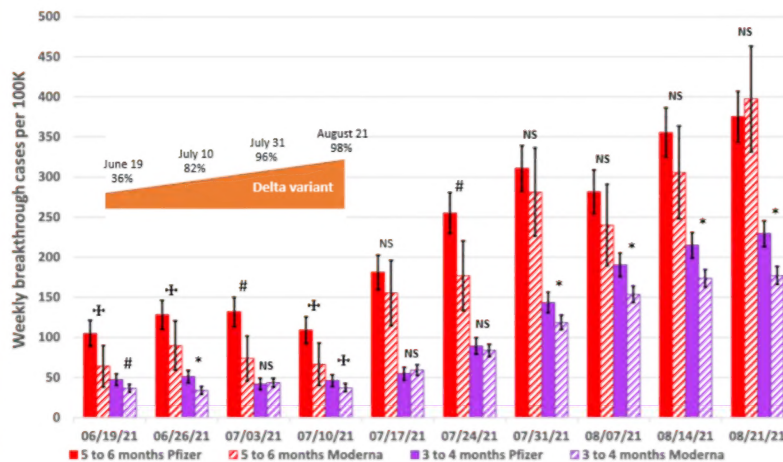


- **Waning immunity are seen with both Pfizer-BioNTech and Moderna** vaccines during Delta phase of the pandemic
- **Moderna vaccine offers better protection than Pfizer vaccine** for individuals vaccinated 4 months prior for weeks ending after July 31

95% CI

| Breakthrough infection rate Pfizer > Moderna | |
|---|---|
| P < 0.001 | * |
| P < 0.01 | # |
| P < 0.05 | ✛ |
| P > 0.05 | NS |

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Total & Breakthrough Hospitalizations in the 65 Years and Older Cohort
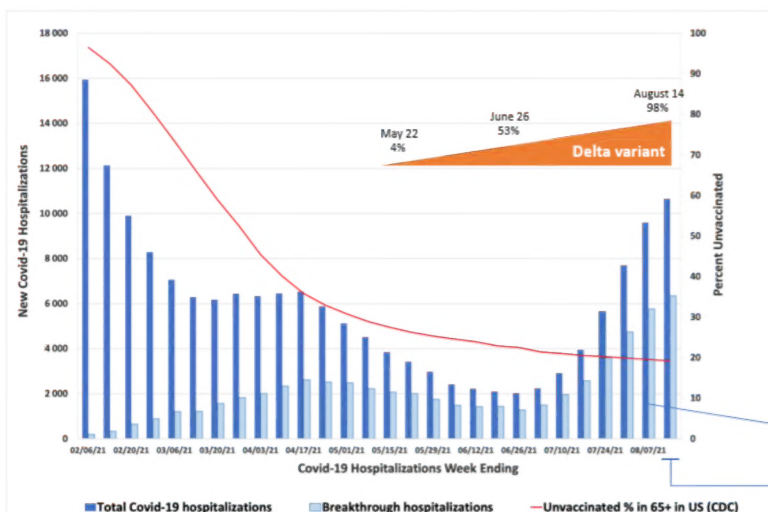
- As Delta variant surged to over 50% in June, COVID-19 hospitalizations more than doubled, reversing the prior trend of decreasing hospitalizations since April
- In this 80% vaccinated 65+ population, an estimated 60% of COVID-19 hospitalizations occurred in fully vaccinated individuals in the week ending August 7th

60% of COVID-19 hospitalizations are in vaccinated individuals

On 08/14/21, data incomplete due to lag in claims processing

Is Vaccine Protection Against Breakthrough Hospitalization Waning Over Time in the 65 Years and Older Cohort?

- VE against breakthrough hospitalization is significantly lower 5-6 months post vaccination than 3-4 months post vaccination

95% CI

Breakthrough hospitalization rate for 5-6 months since vaccination > 3-4 months
$P < 0.001$

How Does mRNA Vaccine Effectiveness in 65+ Salus Cohort with 5.6M Vaccinees Compared to Published Estimates?
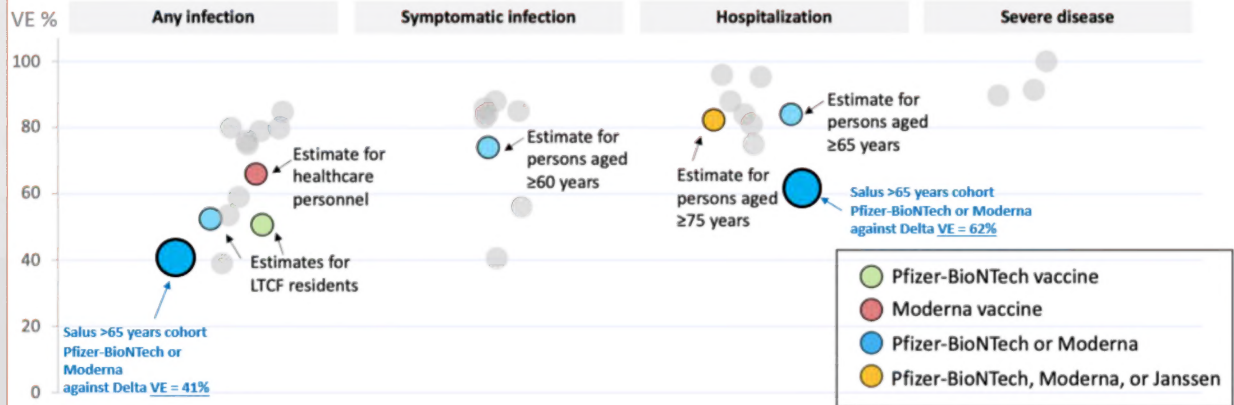
- VE of both mRNA vaccines in this 65+ cohort is lower than previously reported in smaller study sizes for both COVID-19 infection and hospitalization
- VE for mRNA vaccines is higher against hospitalization than against infection

Graphic adapted from CDC Presentation ACIP Meeting August 30, 2021, Oliver, S. Framework for Booster Doses of COVID-19 Vaccines

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Risk Model for Breakthrough Hospitalization
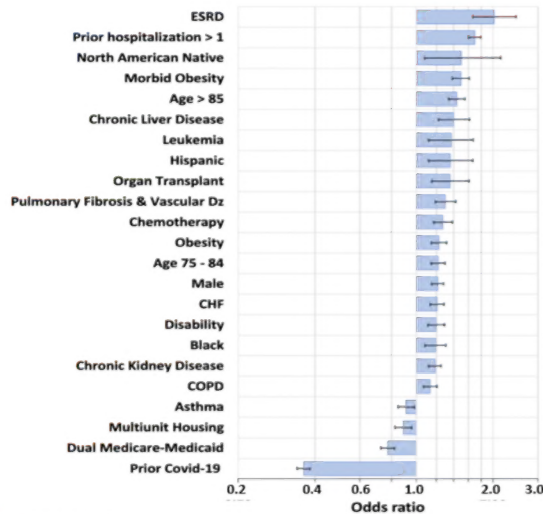
- Risk of breakthrough hospitalization increases with time elapsed since mRNA vaccination with odds ratio increasing to 2.5 at 6 months post vaccination
- Prior COVID-19 infection has a major protective effect against breakthrough hospitalization
- There is a step up in risk in the 75-84 and again in the over 85 age categories compared to the 65-74 category
- Risk model can be used to stratify the over 65 population to best select those in most need of booster vaccine dose

Logistic Regression Model performance:
AUROC 0.73, balanced accuracy 0.67

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